Case Report

Isolated Vascular Lesions (IVL) in Early Allograft Biopsies: A Case Series

Abstract

This case series includes five patients diagnosed as isolated vascular lesion (IVL) on allograft biopsy in an early post-transplant period. These patients presented with graft dysfunction. The biopsies satisfied the criteria for IVL as laid down by Banff 2009. Four of these patients were treated with corticosteroids and other anti rejection measures. C4d and DSA were negative in all. The patients showed good response to treatment with stable graft function at the longest follow-up of one year. We have also reviewed the literature about IVL as a specific entity. There are differences between the molecular and clinical data of IVL. It is difficult to differentiate whether IVL is a rejection or non-rejection process. This study aims to highlight the importance of a rare entity.

Keywords: *Allograft biopsy, C4d, DSA, isolated vascular lesion*

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Introduction

Isolated vascular lesions (IVL) is currently a grey area in renal transplant pathology. Since its first description in 2009,[1] there have been different speculations regarding its pathophysiology. Whether it is a part of antibody mediated or cell mediated rejection or a completely non-rejection process is not clear. According to Banff classification, V lesion can be a part of T cell mediated rejection (TCR) Grade II, III or antibody mediated rejection.[2] However, there are no proper guidelines regarding the treatment or clinical outcome of the isolated V lesions. The study by Sis *et al*.[3] consider IVL as part of TCR while the study by Rabant *et al*.[4] regard these as acute/active antibody mediated rejection (ABMR). Nevertheless, there is a need to recognise IVL as it can be a harbinger of overt rejection episode as opined by Sis *et al*.[3] In this series we present the clinicopathologic features, management and follow up of five patients whose allograft biopsies showed IVL.

Material and Methods

We identified five allograft biopsies showing features of IVL over a period of one year from April 2017 to March 2018. The total number of allograft biopsies done in this period was 122 of which 30 were reported as acute rejection. All these biopsies satisfied the criteria for IVL laid down by Banff 2009.[1] As per these criteria, isolated arteritis is a localised arteritis in the absence of diagnostic tubulointerstitial rejection (Banff type 1 acute TCMR) i.e., interstitial inflammation (i ≤1) and tubulitis (t ≤1). None of these biopsies showed additional morphologic features of ABMR including peritubular capillaritis or thrombotic microangiopathy. C4d was negative in all and so were donor specific antibodies (DSA). The renal biopsy features of all these biopsies are highlighted in Figure 1. C4d was done by immunohistochemistry (HRP-polymer technique) and DSA was performed by bead luminex method.

The maintenance triple immunosupression given after transplant included steroids 20 mg/day, tacrolimus 0.08-0.1 mg/Kg and MMF 600 mg/m^2 body surface area. All these biopsies were done within first week of transplant. The CNI levels were done in all were found to be in normal range between 10-12mg/dl.

Results

Patient 1

44/F unclassified CKD received a renal graft from her mother after dialysis of one year. The HLA was complete match. The cold ischemia time (CIT) was 30 minutes. The surgery was uneventful with on table diuresis. She was kept on maintenance triple

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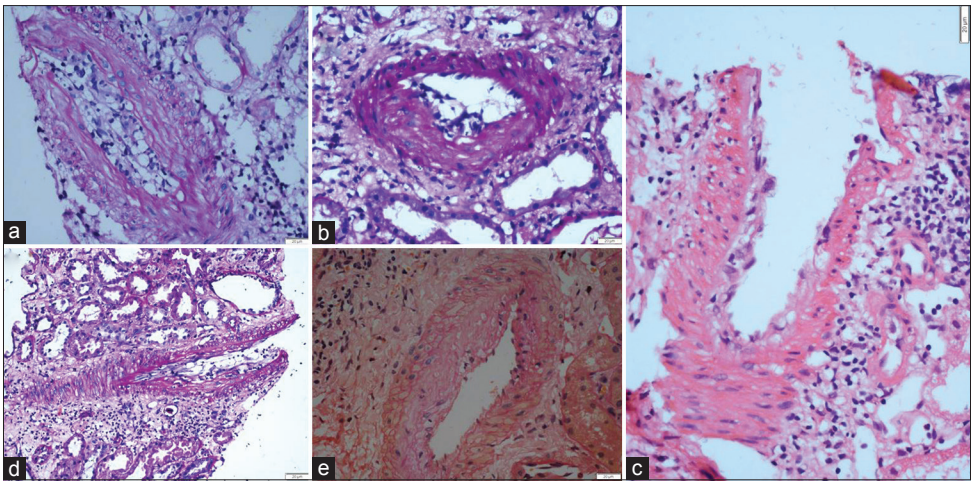

Figure 1: Presence of IVL in the allograft biopsies of all 5 patients

immunosuppression. The creatinine rose to of 1.7 mg/dl on day six of transplant. Allograft biopsy performed showed IVR (v2). She was treated with IV methylprednisolone. She responded to treatment and one year follow up creatinine is 0.8 mg/dl.

Patient 2

A 14 year old male with primary diagnosis of FSGS received a live related graft from father with full HLA match. The CIT was 45 minutes. The patient was kept on maintenance triple immunosuppression and did not receive induction. After a week of transplant the creatinine rose to 1.4 mg/dl and the biopsy showed focal minimal infiltrate of neutrophils in the interstitium with v1 lesion in one of the artery. Incidentally the urine culture showed growth of E coli. The patient was treated only with antibiotic initially followed by IV methylprednisolone. The renal function stabilized with S Cr. of 0.8 mg/dl. His graft function remained normal after a follow up of one year post transplant.

Patient 3

30 Year old lady, HCV positive with unclassified CKD underwent deceased donor renal transplantation, donor being 41 years old lady who met with road traffic accident (RTA). Lymphocyte cross match (LCM) was negative. The warm ischemia time (WIT) was 2 minutes and CIT was 7.25 hours. Patient received Basiliximab 20 mg (2 doses) as induction. Patient had intraoperative hypotension, however recovered on day 0. Patient was started on maintenance triple immunosuppression. Patient developed delayed graft function requiring dialysis on day 3. The doppler study was normal. Renal biopsy on 5th post operative day showed only acute tubular necrosis with negative c4d. The renal function did not recover and a repeat biopsy was performed on 9th post operative day (POD) showed isolated vascular rejection (IVR) (v1). She was treated with IV methylprednisolone followed by ATG, plasmapheresis (5 sessions) and high dose IVIg. Patient recovered with stable graft function at 9 months follow up period.

Patient 4

27 year old male, HCV positive patient with unclassified CKD underwent deceased donor renal transplantation, donor being 24 years male who met with RTA. LCM was negative, W.I.T 3.5 minutes and C.I.T 7.5 hours. Patient received Basiliximab 20 mg (2 doses) as induction. Patient was started on triple immunosupression. Patient developed delayed graft function requiring dialysis on day 5 and doppler study was normal. Renal biopsy on day 8 revealed IVR-(v2). He was started on IV methylprednisolone followed by plasmapheresis (5 sessions) and high dose IVIg. Patient recovered on day 23. At present patient is 6 months post-transplant with stable graft function (S.Cr-1.1 mg/dl).

Patient 5

31/M with unclassified CKD on dialysis for 3 years and HCV seropositive received a cadaver donor graft with CIT of 7 hours and WIT of 10 minutes. He received induction basiliximab and was kept of triple immunosupression. The serum creatinine on 3rd POD was 5.9 mg/dl. The renal biopsy showed IVR (v1). He was treated with five sessions of plasmapheresis and intravenous methylprednisolone. Repeat biopsy done on POD 11 showed increased inflammation (i3), glomerulitis (g2) and peritubular capillaritis (ptc2). At this point he was given IVIG and high dose ATG. The serum creatinine came down to 0.6 mg/dl. However, patient further developed acinetobactor pneumonia and also CMV infection. He was treated effectively and on follow up of 9 months his graft function is stable with serum creatinine of 1.1 mg/dl.

Discussion

The present study aims to focus on isolated vascular lesions which were identified in very early post-transplant period

in patients presenting with graft dysfunction. Sis *et al*. has reported 103 patients of IVL in one of the large multicentre collaborative study.[3] In this study IVL was identified in early POD with median duration of 42 days. The risk of graft failure was identified to be 3.51 fold higher than negative controls. However, most of the patients responded to corticosteroids and T cell deletion therapy with reduced risk of transplant failure at 3 and 8 years. Owing to the response to anti T cell therapy and negative C4d, IVL was thought to be a T cell mediated rejection. Though all our biopsies were c4d and DSA negative, four of the five patients were treated aggressively with combined measures for T cell as well as antibody mediated rejection. This could be because of awareness and introduction of C4d negative ABMR by Banff classification.[5] About 20% patients of IVL in the study by Sis *et al*.[3] did not respond to T cell depletion therapy and corticosteroids. It is difficult to rule out an underlying antibody mediated component in these patients.

There are various speculations regarding the pathogenesis and behaviour of IVL. Muller *et al*. in their microarray based analysis could not find association of IVL with gene expression for T cells, interferon-γ and tissue injury and concluded IVL to be of uncertain significance.[6] Since IVL has been identified in very early post-transplant period with DGF, it has also been thought to be a form of ischemic injury.[7] A large transcriptome analysis performed on early IVL (referred as eIV) showed them to have weak immune signatures in comparison with TCMR and were comparable to normal findings.[8] This questions the association of IVL with rejection as proposed by Banff and perhaps molecular signatures are necessary in early IVL with negative C4d and DSA. Unfortunately it is not practical and possible to have an exhaustive molecular analysis when dealt with a clinical situation of graft dysfunction in a very early postoperative period. The treatment in these settings is largely guided by clinical judgements and it is imperative that that these lesions are treated as acute rejection.

Salazar *et al*.[9] have studied the microarray based molecular testing in 703 indicated biopsies to understand the association of IVL with rejection. IVL showed TCMR scores in 21% cases whereas ABMR scores in 46% of cases. Early isolated v-lesion specimens had no molecular signatures of acute rejection and were DSA negative whereas the ones after 1 year of transplantation had positive DSA and ABMR scores. Salzar *et al*. conclude that v-lesions in indication biopsy specimens do not affect prognosis and can reflect TCMR, ABMR, or no rejection. However, as opined by Salazar *et al*., we may be unaware of some yet unknown forms of rejection which may be accompanied by vascular lesions. Molecular analysis was also not feasible in our set up.

The effective immunosupression used in the current era is responsible for the significant drop in the early cellular rejection episodes. It is possible that the component of tubulitis was addressed by this therapy leaving alone the vascular lesions. This unresponsiveness of vascular lesions to the routine immunosuppression protocol reflects the aggressiveness of the vascular rejection. Some studies tried to evaluate the relation of IVL with ABMR. Rabant *et al*.[4] have elaborately studied this aspect and reported a negative relation between IVL and ABMR. However they have insisted evaluation of DSA in all IVL cases as this could evolve into severe ABMR in future. The type of transplant also influences IVL. Some studies have found higher proportion of IVL cases in deceased donor grafts.

The literature about IVL is evolving and does not point towards one particular aetiology. Overall the clinical data favours IVL as a part of rejection process and warrants anti rejection measures particularly when associated with graft dysfunction. The present case series cannot comment upon the long term graft function in these patients. It was definitely observed that graft function improved with increased immunosuppression and antirejection treatment. The study aims to highlight the clinical importance of finding IVL in early allograft biopsies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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